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HISTOPATHOLOGICAL FEATURES OF TESTICULAR REGRESSION SYNDROME: RELATION TO PATIENT AGE AND IMPLICATIONS FOR MANAGEMENT

H. Law, I. Mushtaq, K. Wingrove, M. Malone, and N. J. Sebire ☐ *Departments of Histopathology and Urology, Great Ormond Street Hospital, London, United Kingdom*

☐ *Testicular regression syndrome (TRS) represents a congenital condition in which no normal testicular tissue can be identified following exploration for a clinically impalpable testis. A spectrum of pathological findings may be present but there is little literature systematically examining these features. We searched a pediatric histopathology database to identify cases of TRS, and the histopathological findings were reviewed and pooled with those of all previously published smaller series. A total of 117 cases were identified during the period (1989–2004), median age 2 (range birth–12) years. In 52 (44%) a nodule was identified macroscopically, median maximum diameter 0.5 (range 0.1–2.0) cm. Microscopic hemosiderin-laden macrophages were present in 85 (73%), dystrophic calcification in 52 (44%), residual testicular tubules in 12 (10%), vas deferens in 71 (61%), and epididymal tissue in 39 (33%). The prevalence of hemosiderin laden macrophages and dystrophic calcification were significantly greater in cases ≤3 years (84% versus 64% and 55% versus 32%, respectively). But there was no significant difference in the frequency of other findings between the younger and older age groups; in particular, the presence of residual testicular tubules was similar (7% versus 13%, respectively). Furthermore, there was no significant correlation between identification of a macroscopically distinct nodule and presence of residual tubular structures, tubules being identified in 6 of the 65 cases in which no clearly identifiable nodule was seen macroscopically. The presence of hemosiderin-laden macrophages and foci of dystrophic calcification showed a positive association. TRS is associated with specific histopathological features, the findings being consistent with changes secondary to intrauterine testicular torsion. Residual testicular tubules are found in 10% of cases regardless of the presence or absence of a macroscopically identifiable nodule.*

Keywords testicular regression syndrome, testis, vanished

Address correspondence to Dr. N. J. Sebire, Department of Histopathology, Camelia Botnar Laboratories, Great Ormond Street Hospital, Great Ormond Street, WC1N 3JH, UK. E-mail: SebirN@gosh.njs.uk

INTRODUCTION

Exploration of the scrotal/inguinal region for histological identification of an impalpable testis is a relatively common indication for tissue submitted to a pediatric histopathology department. The clinical management of the impalpable testis is well described in pediatric urology texts and is based essentially on exploration of the anatomical region through which the testis normally descends [1]. The rationale for identification of an intra-abdominal testis in an XY male is based on the previously reported increased risk of development of subsequent malignancy if the testis is left in an ectopic, intra-abdominal position [2]. In a proportion of such cases, no identifiable testis will be found following laparoscopic or open surgical exploration, but a nodule or strand of tissue may be present close to spermatic cord structures, which is excised for histopathological examination for identification of residual testicular tissue. This absence of a testis, usually unilaterally, in an otherwise normal 46XY male has been termed "vanishing testis" or "testicular regression syndrome" and is thought to be a consequence of intrauterine or perinatal torsion or infarction.

Testicular regression syndrome (TRS) is characterized anatomically by a rudimentary spermatic cord with absence of macroscopically identifiable testicular tissue. There is limited literature describing in detail the histopathological findings encountered in a large series of such cases, and no studies have attempted to address the relationship of such histopathological features to patient age at examination. The aim of this study is to describe therefore the main histopathological features in a large series of pediatric cases derived from a tertiary pediatric histopathology unit in which the diagnosis of vanished testis/TRS was made.

METHODS

The Department of Histopathology, Great Ormond Street Hospital, London, is a tertiary referral pathology unit examining specimens both from patients referred to the hospital for surgical intervention and histopathological material referred from other hospitals. A search of the histopathology database was made to identify all cases of surgical material with a final diagnosis of vanished testis or TRS. The search was conducted on the basis of SNOP/SNOMED codes and a free text search for "vanished AND testis" OR "testicular AND regression" anywhere in the report. In all the cases, basic clinical details provided and histopathological findings were reviewed. Cases were anonymized and identified only by study number. The study was approved by the local Research Ethics Committee. The histological findings were reviewed with particular regard to the presence or absence

of testicular material, the presence or absence of hemosiderin-laden macrophages, and any presence or absence of components of the spermatic cord.

Since the main outcome data are categorical, to determine whether there was a significant effect of patient age on the histological findings, cases were dichotomized into those less than 3 years of age, or those 3 or more years of age; comparison of the frequencies of histological findings between these groups were carried out using comparison of proportions test (modified Fisher exact test). Spearman rank correlation was used to assess the significance of correlation between the histopathological findings within the total group.

RESULTS

During the study period (1988–2004), the search identified 117 cases of TRS, accounting for 21% of the 551 testicular/paratesticular surgical specimens examined during this period. The clinical information provided in the cases was "impalpable testis," "testicular remnant," or "vanished testis." The median (range) age at examination was 2 (birth-12) years. The characteristic histopathological features encountered included a fibrovascular nodule with associated spermatic cord remnants, absence of well-formed testicular tubular structures in most cases, and the presence of areas containing scattered hemosiderin-laden macrophages and/or calcification (Figures 1–5). The relative frequencies of the histopathological findings are provided in Table 1 and Figure 6. A fibrovascular macroscopically identifiable nodule was present in 44% of cases, well-formed spermatic cord vascular remnants in 37%, epididymal structures in 33%, and residual vas deferens in 61%. The nodule, where present, measured median 0.5 cm diameter (range 0.1–1.9 cm). Identifiable testicular tubular tissue was present in only 10% of cases, usually represented by areas of bland fibrosis with scattered tubules.

No atypical germ cells were identified morphologically in any case and indeed, in the majority of cases in which testicular tubules were present, these showed a Sertoli cell-only phenotype on light microscopy. Hemosiderin-laden macrophages within fibrous connective tissue were identified in 73% of all cases, ranging from scanty to highly prominent in number, and areas of dystrophic calcification were seen in 44%.

Patient age was available for 108 specimens: 55 were <3 years of age, and 53 ≥ 3 years of age at surgery. The prevalence of hemosiderin-laden macrophages and dystrophic calcification were significantly greater in the younger patient group (84% versus 64% and 55% versus 32%, respectively; $z = 2.31$, $p < 0.02$ and $z = 2.35$, $p < 0.001$, respectively). There was no significant difference in the frequency of other findings between the younger and older age groups, in particular, the presence of residual testicular

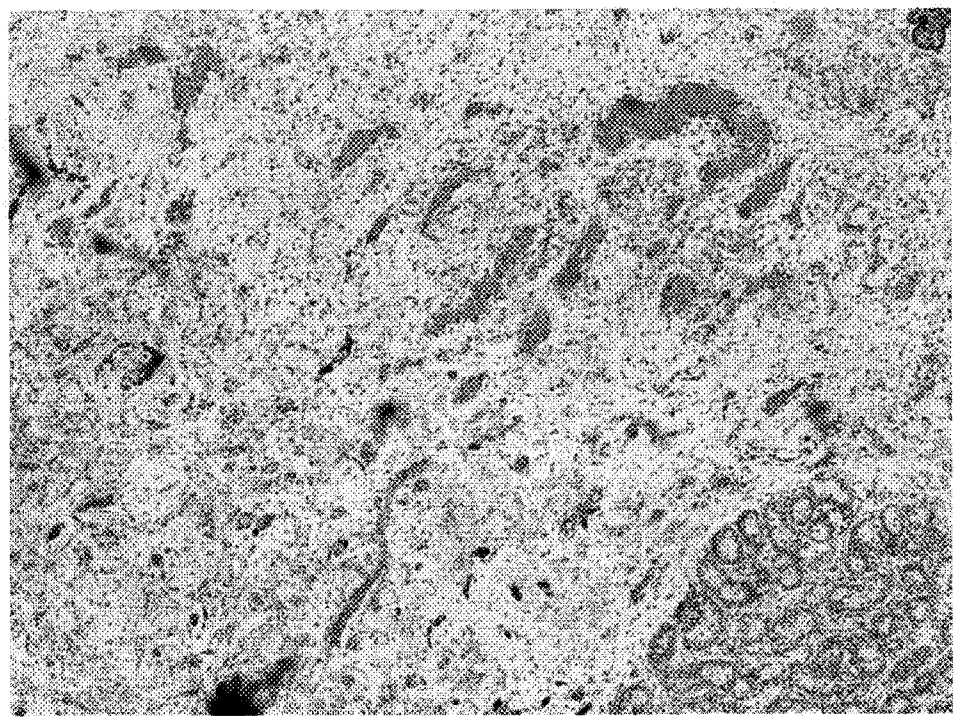

FIGURE 1 Photomicrograph of a case of pediatric testicular regression syndrome demonstrating residual fibrous nodule with dystrophic calcification and an area of residual tubules (bottom right; H&E, original magnification ×40).

tubules was similar (7% versus 13%, respectively; $z = -1.02$, $p = 0.24$). Furthermore, there was no significant correlation between identification of a distinct nodule and presence of residual tubular structures ($p = 0.69$), tubules being identified in 6 of the 65 cases in which no clearly identifiable nodule was seen macroscopically. The presence of hemosiderin-laden macrophages and foci of dystrophic calcification showed a positive association with each other ($t = 2.2$, $p = 0.03$).

DISCUSSION

This study has reported in detail the histopathological features encountered in TRS across the age range of infancy and childhood. The majority of cases were submitted for histopathological examination before 4 years of age for the indication of exploration of a unilateral impalpable testis. The major histopathological criteria for the diagnosis are the absence of normal testicular tissue and the presence of remnants of various spermatic cord and testicular structures in association with abnormal fibrous connective tissue, which often also demonstrates scattered hemosiderin-laden

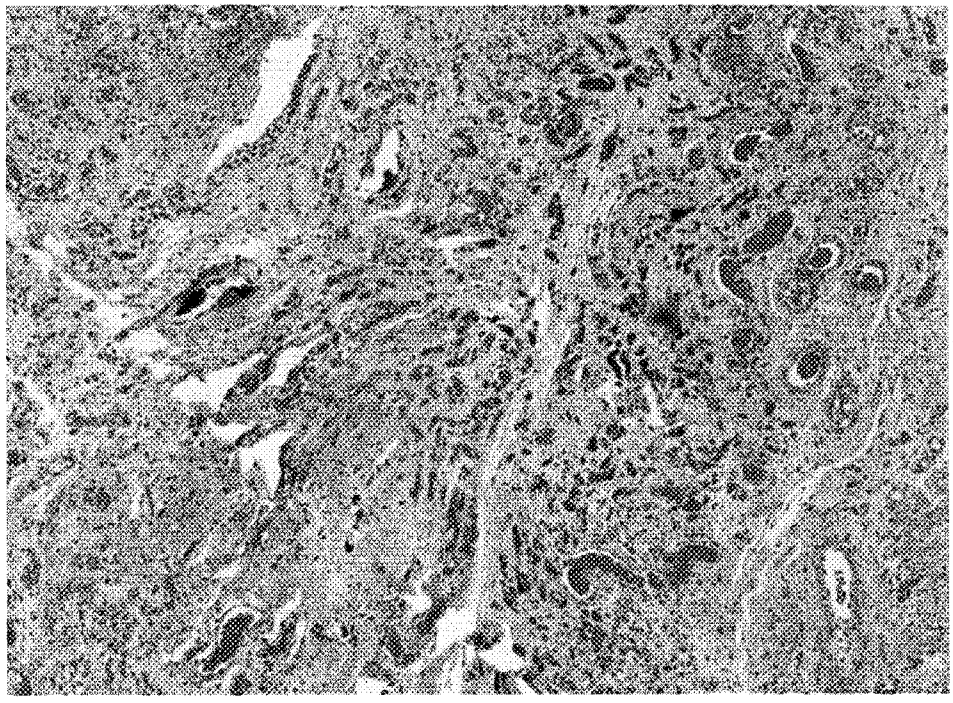

FIGURE 2 Photomicrograph of pediatric testicular regression syndrome showing a residual fibrous nodule with dystrophic calcification and numerous hemosiderin-laden macrophages (H&E, original magnification ×25).

macrophages and dystrophic calcification. These findings, in general, are similar to those of previous studies that have described spermatic cord-like structures with a small mass of firm, fibrotic tissue at one end with vas deferens and vessels usually present [3]. However, we have further defined the relative frequencies of these features and their relationship to age at examination. Residual testicular tubules are only rarely encountered (<10% of cases); their prevalence is unrelated to patient age. Although some of the features noted above are not age-related, hemosiderin-laden macrophages and calcification are significantly more commonly encountered in younger patients.

The combined data from the current, largest available study, and previous reports documenting the presence or absence of histological features in testicular regression syndrome [3–8], are provided in Table 2 (Figure 7). These pooled data indicate that a distinct nodular structure is present in only about half the cases submitted for histopathological examination and residual testicular tubules are identified histologically in only 6% of cases. Vas deferens and hemosiderin-laden macrophages are the most common findings. Despite the presence of scattered residual seminiferous tubules,

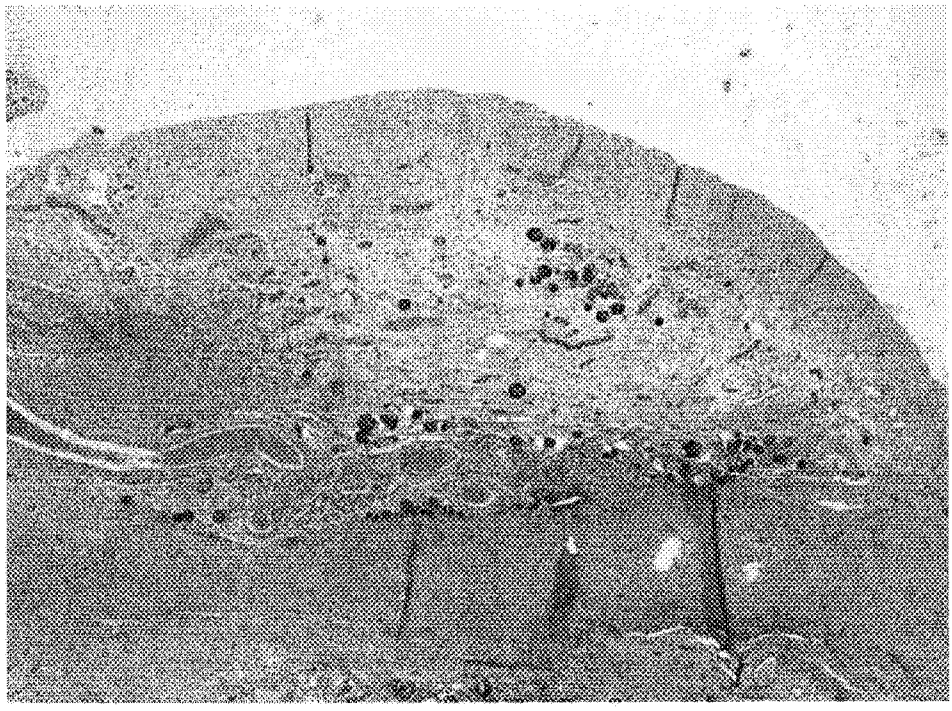

FIGURE 3 Low power photomicrograph of pediatric testicular regression syndrome demonstrating a residual fibrous nodule with tubules, dystrophic calcification, and prominent vessels (H&E, original magnification ×12).

no cases thus far reported have noted atypical tubular germ cells. Indeed, on light microscopy alone, the majority of publications, including the present one, suggest that when tubules are present these appear to be Sertoli cell only with no identifiable germ cell component. Although the risk of subsequent development of testicular germ cell neoplasia is significantly increased in the presence of cryptorchidism [2], the risk associated with residual testicular tubules as a component of TRS remains unknown. We are not aware of any reported cases of confirmed intratubular germ cell neoplasia (ITGN) or invasive germ cell malignancy documented to be arising in a nodule of "regressed testis."

The present histopathological study examining these specimens also would suggest on empirical grounds minimal risk of malignant complications. Controversy remains among pediatric urologists regarding the appropriate management of such cases, in particular the extent of surgical exploration and need for surgical removal if TRS is suspected [9].

The association between patient age at surgery and the prevalence of histological findings allows some conclusions regarding the underlying pathophysiological process. The lack of significant association between

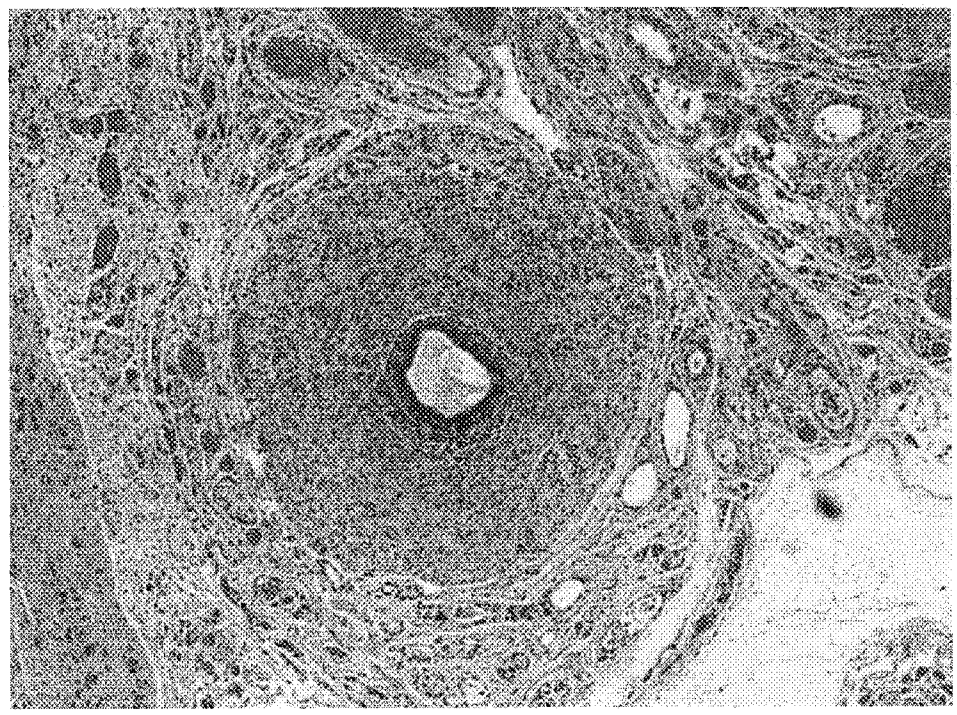

FIGURE 4 Photomicrograph of pediatric testicular regression syndrome showing residual vas deferens (H&E, original magnification ×100).

the frequency of detecting residual testicular tubules and patient age at surgery suggests that a severe insult occurs during intrauterine life with no ongoing process of tubular damage once the episode has resolved. Furthermore, the increase in prevalence of hemosiderin-laden macrophages and dystrophic calcification in younger patients also supports the suggestion of an ischemic insult resulting in significant tissue damage and hemorrhage followed by an influx of macrophages, the number of which then gradually diminishes with time. In conjunction, these findings are entirely consistent with the hypothesis that TRS is the result of intrauterine testicular ischemia, most likely caused by torsion, occurring as an acute event during fetal development. The lack of association of frequency of residual testicular tubules with either patient age or presence of a macroscopically identifiable nodule indicates that surgical removal of any tissue at the end-point of the spermatic cord structures is the only way to ensure with certainty that no residual tubules remain in an intra-abdominal location, with their potential risk of subsequent germ cell malignancy development.

In contrast, in this study and all other published series, residual tubules are rarely encountered and, where present, appear predominantly composed of Sertoli cells with no abnormal germ cells suggestive of intratubular

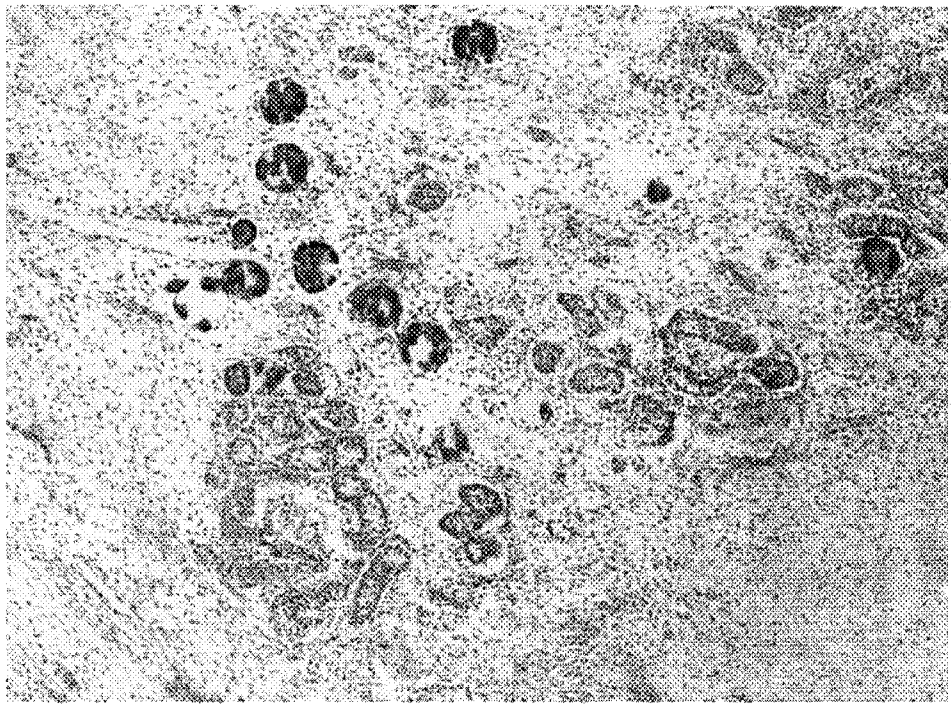

FIGURE 5 Photomicrograph of pediatric testicular regression syndrome demonstrating residual fibrous tissue with dystrophic calcification and an area of residual tubules (H&E, original magnification ×40).

germ cell neoplasia. This suggests that the risk of germ cell malignancy development in such cases must be exceedingly small. The findings of this study do not allow resolution of the dilemma regarding optimal clinical management of such cases.

Since the histopathological features suggest that TRS is probably a consequence of testicular ischemia/infarction, most likely secondary to intrauterine torsion during descent, it is interesting to examine the association with possible predisposing factors. Data regarding laterality were not available in our series; however, several clinical studies have reported that

TABLE 1 Histological Features in a Series of 117 Cases of Testicular Regression Syndrome Examined at a Single Pediatric Pathology Department

Feature	Number	Percent	95% Confidence interval
Nodule	52	44	35–54
Hemosiderin-laden macrophages	85	73	64–80
Calcification	52	44	35–54
Residual tubules	12	10	01/05/17
Vas deferens	71	61	51–70
Epididymis	39	33	25–43
Spermatic cord vessels	43	37	28–46

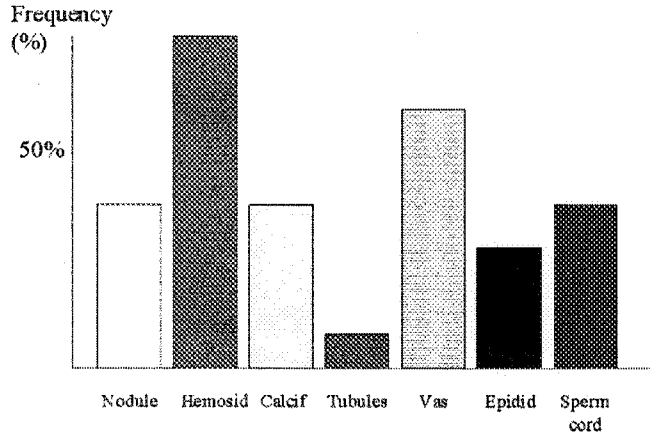

FIGURE 6 Frequencies (%) of various histopathological features in a series of 117 cases of pediatric testicular regression syndrome. Residual testicular tubules were identified in less than 10% of cases. [Hemosid = hemosiderin-laden macrophages, calcif = calcification, epidid = epididymal structures, sperm cord = spermatic cord vascular structures].

the testis is much more commonly absent on the left side [8, 10, 11]. Interestingly, the prevalence of testicular torsion also is more common on the left, and it has been suggested that as the left testis descends into the scrotum at an earlier stage than the right, it may be at greater risk of both torsion or other traumatic damage [12].

In the vast majority of cases, TRS appears to be a sporadic occurrence, and the patients are otherwise normal with no significant family history. However, there are now several reports of TRS either in association with other defects, including severe mental retardation in chromosomally normal siblings [13], or occurring in several members of the same family, suggesting a possible genetic basis for the condition in some subjects [14]. Furthermore,

TABLE 2 Data on Histopathological Features of Vanished Tests in Series Reporting on More Than 10 cases in the Literature

Study	Number	Nodule (%)	Tubules (%)	Vas (%)	Epididymis (%)	Hemosiderin (%)	Calcification (%)
Present study	117	44	10	61	33	73	44
Nishizaw et al. [8]	43	63	5	72	26	–	–
Spires et al. [7]	13	85	0	69	38	69	62
Grady et al. [6]	14	–	7	–	–	93	–
Cendron et al. [5]	29	100	0	72	28	86	83
Merry et al. [4]	47	23	9	68	–	–	15
Smith et al. [3]	77	–	4	79	36	42	42
Total	340	52	6	69	33	66	43

The pooled weighted prevelences with 95% confidence intervals for each parameter are provided in Figure 7.

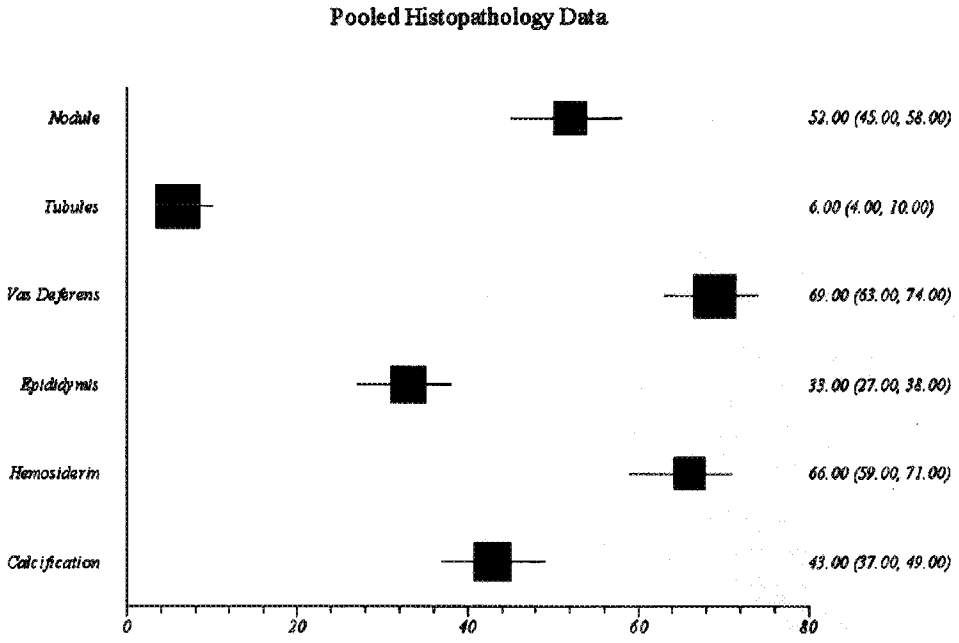

FIGURE 7 Summary data from the results of pooled studies reporting on the histopathological features of 340 cases of testicular regression syndrome. Boxes represent mean, lines 95% confidence intervals (Table 2).

although uncommon, the phenotypic spectrum associated with TRS may vary from normal male with unilateral impalpable testis, as in the cases in this series, through phenotypic male with micropenis, to phenotypic female. The phenotype presumably is related to the extent and timing of the intrauterine event in relation to sexual development [15].

Clinically, a unilateral impalpable testis may be associated with TRS, cryporchidism, retractile testis, or testicular agenesis, and laparoscopy is widely used to distinguish among these conditions while avoiding open abdominal surgery. When vas and spermatic vessels are visualized exiting the internal inguinal ring on laparoscopy in the setting of a nonpalpable testicle, a groin exploration may be carried out to identify and remove the testicular nubbin associated with a vanished testis.

SUMMARY

This study has described in detail the histopathological features of TRS, highlighting the important clinical features of this condition and discussing the salient histopathological findings. Residual testicular tubules are found in $<10\%$ of cases, their prevalence being unrelated to age at surgery. The most characteristic findings are presence of a fibrovascular nodule with

associated hemosiderin-laden macrophages and dystrophic calcification. These features are more commonly detected in younger pateints, consistent with the hypothesis that TRS is a consequence of intrauterine testicular torsion. Intratubular germ cell neoplasia was not identified in any case.

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